REMARKS

According to applicants' last response, Claims 1, 4-7, 9, 10, 13-16 and 19-21 were pending.

According to the examiner, only claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20 are being examined. As noted in Section I, below, Applicants do not understand the basis for the withdrawal of claims 6, 15 and 21 and believe these claims should remain pending.

Thus Applicants believe that claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20 should be pending and examined. Claims 1, 9 and 16 have been amended.

It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. Applicants respectfully submit that their application is now in condition for allowance.

I. Miscellaneous

Th Examiner withdrew claims 6, 15, 21 for being multiply dependent without explaining why. None of these dependencies are to withdrawn or cancelled claims. Therefore, Applicants request an explanation of why the examiner is withdrawing these claims and why they would need to be properly amended in order to be rejoined (and included in the rejection). Applicants consider these claims to be pending and under examination as they are in proper form.

II. Rejections Under 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner maintained the rejection of claims 1, 7, 9-10, 16 due to lack of "a clear written description of an organic small molecule inhibitor of MAPK/ERK kinase enzymes" for reasons of record.

Applicants reiterate the proper legal standard for a rejection based on inadequate written description set forth in their prior response (without repeating it here).

B. The Rejection

Applicant's arguments set forth in paper of 12/05/03 were considered but not deemed to be persuasive for the following reasons:

The Office contends that "**a definition by function alone does not suffice to define the genus**" because it is only an indication of what the genus does, rather than what it is (citing *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Applicants will not repeat the citation found in the Office Action.

The Action notes that the limitation argued by Applicants are not in the claims. This limitation was characterized by Applicants as a common feature that sets the small molecule inhibitors of the invention apart as a genus/subgenus from nearly all other kinase inhibitor: they are noncompetitive inhibitors of MEK and share a common (or overlapping) binding site in MEK vs nearly all other kinase inhibitors - which are ATP-competitive,

C. Applicants' Response

Applicants maintain their position that the Office has not met its burden, as noted above, for a *prima facie* case of lack of adequate written description and that the Office's reliance on the *Lilly* case and the use of analogies to DNA sequences are not applicable to the present case.

However, in order to move this case to allowance, Applicants have amended thee relevant claims to recite limitations that distinguish these inhibitors as a genus or class of MEK inhibitors.

Applicants will not restate their discussion of the key elements of the present invention noted in the last Response. Suffice it to say here that

(1) the small molecule inhibitors elected here are all inhibitors of the MEK enzyme

(2) Inhibition of MEK action disrupts MAPK pathway

(3) This has an unexpected outcome in melanoma cells particularly human melanoma cells, causing them to undergo apoptosis and die. The inhibitors are thus cytotoxic.

(4) The present small molecule inhibitors are all **noncompetitive** inhibitors of MEK, so that they do not inhibit the binding of the enzyme to one of its substrates, adenosine triphosphate (ATP), which is the source of the phosphate group that is transferred to the other MEK substrate, the MAPK/ERK protein.

(5) Although not included as an additional limitation in the presently amended claims (as Applicants believe the limitation based on (4) above are sufficient), where studied, these MEK inhibitors share a common/overlapping binding site in MEK (Favata, M.F. et al., J Biol Chem. 1998, 273:18623-32 ("Favata"), now of record and acknowledged by the Examiner.

Applicants respectfully remind the Examiner that the **noncompetitive** mode of inhibition of all the small molecule inhibitors described and claimed herein was well-known in the art as a common feature that sets them apart as a genus or subgenus from nearly all other kinase inhibitors which are ATP-competitive (Cohen, P., *Curr Opin Chem Biol.* 1999, *3*:459-465, now of record and acknowledged by the Examiner). The compounds PD184352, PD98059 and U0126, are a group of

kinase inhibitors that are direct, but noncompetitive, inhibitors of MEK (Favata, *supra*, and Sebolt-Leopold, J.S. *et al.*, *Nature Medicine*, 1999, *5*:810-816, also of record in this case).

In view of these amendments and the foregoing remarks, the claims comply with the written description requirement of 35 USC § 112, first paragraph. The grounds for rejection may properly be withdrawn.

III. Rejection Under 35 U.S.C. § 112, First Paragraph - Lack of Enablement

The Office maintained rejection of claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20 for lack of enablement of a method of killing melanoma for reasons of record. Applicants reiterate the proper legal standard for a rejection based on lack of enablement set forth in their prior response (without repeating it here).

The Office Action points to a number of Applicant's prior arguments

1. The inventors found that sustained inhibition of MAPK signaling in human melanoma cells produced by inhibiting MEK enzymatic activity, resulted in a melanoma-selective apoptotic and cytotoxic response. Applicant asserts that this provides an adequate basis for claims having the present scope.

As acknowledged by the Office, Applicants described how the Sebolt-Leopold reference (*supra*) discloses that PD184352 , inhibited MEK and the MAP kinase pathway, resulting in a therapeutic outcomes including impairment in the growth *in vivo* of mouse and human colon tumors.

2. As stated in the Action, Applicant asserted that they identified a different tumor type, melanoma, which depends on MAPK activation for survival and concluded that this leaves little room for doubt as to the effectiveness and selectivity that would be expected of PD184352 and the other disclosed MEK inhibitors in (a) killing melanoma cells, (b) mediating an antitumor response in a subject with melanoma, and (c) inhibiting growth (and recurrent growth) of melanoma in a mammal.

3. The Action stated that Applicants assert that the above effects would be expected to be selective for melanoma and sparing of normal melanocytes based on the inventors' showing that MEK inhibition does not kill normal human melanocytes, even though it completely blocks the activation of MAPK in these cells, arresting them in G1. Applicants could observe no apoptosis even after prolonged inhibition (specification at page 4, lines 26-29).

4. The Action stated that Applicants described their observation that MEK inhibition stimulated melanin production in melanoma cells thus mimicking a phenotype associated with differentiated melanocytes. Applicants asserted that cAMP-elevating agents are known to induce differentiation accompanied by melanin production in melanoma cells. Applicants noted that although two cAMP-elevating agents synergize with MEK inhibitors in their stimulation of melanin production, both cAMP-elevating agents dominantly antagonized the apoptosis induced by MEK inhibitors (page 4, lines 20-25; see also, Example 1V). This should put to rest the concern and confusion expressed in the (prior) Office Action with regard to the existence of a correlation between "specific levels of reduction of ERK1/2 enzymes . ..but not <u>any</u> level of reduction" and apoptosis *in vitro*.

5. Applicants stated that "there is no such thing here: MEK inhibition kills melanoma cells, and concomitant elevation of cAMP in these cells antagonizes this effect. The specification showed clearly that apoptosis in melanoma cells was not a mere "byproduct" of the differentiation induced by inhibiting MAPK signaling (*e.g.* page 48, lines 25-28; Figs. 5A, 5B, 6 and 8; Example IV, page 48, lines 17-18)."

The Action goes on to try to refute Applicant's position as is indicated in the sections below. Applicants have italicized and underscored certain terms to emphasize them (and distinguish the emphasis from the "bolding" used by the Office in one place). The Examiner's assertions and detailed analysis of experimental data, reflected in some of these italicized terms, amount to a somewhat unclear and rather uncharacteristic "scientific review," as if by a research grant reviewer or journal referee. The Action does not meet the appropriate legal standards required by the law of enablement.

A. "The data presented in the specification indicates that 1) there is no correlation between the inhibition of the MAPK pathway at <u>*any reduced level*</u> of ERK1/ERK2, and apoptosis in melanoma cells *in vitro*, and that a <u>*certain specific*</u> level of ERK1/ERK2 enzymes of the MAPK pathway seems to be required for the occurrence of apoptosis in melanoma cells *in vitro*."

B. "From Figure 9, and the disclosure in the specification on page 48, lines 20-23, it is clear that although IBMX alone does not reduce the level of ERK1/ERK2, and although PD8059 alone reduces the level of ERK1/ERK2, IBMX together with PD8059 <u>*further reduces*</u> the level of ERK1/ERK2, and abolishes the apoptosis effect of PD8059 in melanoma cells *in vitro*. The specification <u>*specifically*</u> discloses that <u>*partial inhibition of activation*</u> of ERK1/ERK2 by PD8059

is sufficient to trigger apoptosis in melanoma cells *in vitro*, and that **greater degree of inhibition** of activation of ERK1/ERK2 produced by the combination of PD8059 and IBMX is *not apoptotic* (emphasis added)."

C. "Thus , there is no indication that there is a correlation between the inhibition of the MAPK pathway, *at any reduced level* of ERK1/ERK2, and apoptosis in melanoma cells *in vitro*, because if there is a correlation between the inhibition of the MAPK pathway *at any reduced level* of ERK1/ERK2, and apoptosis, *one would expect* that apoptosis would be enhanced in melanoma cells in the presence of both PD8059 and IBMX, in view of the fact that the level of ERK1/ERK2 is *significantly reduced in the combined presence* of both PD8059 and IBMX."

D. "This lack of a correlation between apoptosis and *the any reduced level* of ERK1/ERK2, or *the requirement of a specific level* of ERK1/ERK2 for the occurrence of apoptosis, is further substantiated by the fact that in normal melanocytes, apoptosis does not occur in the presence of PD8059, even though PD8059 does reduce the level of ERK1/ERK2 in normal melanocytes cells."

E. "Further, it is not clear *how and why IBMX synergizes* with PD8059 in stimulation of melanin production, nor is it clear *how and why IBMX abolishes apoptosis* induced by PD8059, especially in view that it is well known in the art that *apoptosis is a complex phenomena*, involving several proteins, such as proteins of the Bcl family, and the proteins of the caspases family, *etc.*"

F. "Thus Applicant has not shown that there is a correlation between *any reduced level* of ERK1/ERK2 and apoptosis in melanoma cells *in vitro*, in view of the synergistic effect of IBMX and PD8059 on reduction of the level of ERK1/ERK2, and the abolishment by IBMX of apoptosis induced by PD8059."

> *Applicant's Comment: The "hows" and the "whys" noted above are not relevant to the enablement analysis, considering that the claims do not involve IBMX, its synergism with PD8059, or stimulation of melanin production, and the interplay of the foregoing with apoptosis, regardless of its complexity.*

G. "The synergistic effect of IBMX and PD8059 on the reduction of ERK1/ERK2 levels and the fact that IBMX abolished the apoptosis induced by PD8059 are an indication that the Applicant has not shown the existence of a correlation between any *particular reduced level* of ERK1/ERK2 and the occurrence of apoptosis in melanoma cells *in vitro.*"

H. "It is noted that although administration of PD184352, which inhibits MEK and thereby the MAP kinase pathway, results in the impairment in the growth *in vivo* of mouse and

human colon tumors, this *cannot apply to melanoma* cells, because *different cancer cells have different etiology and characteristics*, and one cannot predict that melanoma cells would react the same way to PD184352 *in vivo."*

> *Applicant's Comment: The blanket, nonspecific, statements above from the Office Action are not legally supported here. Applicants assert that if an agent which is merely cytostatic to colon cancer cells (in vitro or in vivo) impairs growth of mouse and human colon cancers in vivo, then it is logical, and would clearly be predictable, that an agent that is cytotoxic, and actually kills melanoma cells, not merely slows their growth, would impair growth of melanomas in vivo.*

I. "Thus, in view that only *a certain specific level* of reduction of ERK1/2, enzymes of the MAPK pathway, *but not any level of reduction* of ERK1/2, seems to be correlated with apoptosis in melanoma cells *in vitro*, and because of possible *homeostasis regulation, which is a common phenomena in vivo*, one cannot predict that PD184352 would reduce ERK1/2, enzymes of the MAPK pathway, *to a specific level* in melanoma cells in *vivo*, effective for inducing apoptosis of human melanoma cells *in vivo*."

> *Applicant's Comment: The constant return to these "certain specific level", and "not any level" statements of the Office Action are not only unclear in their intent, but appear to represent a preoccupation with mechanism, rather than with demonstrated effects on killing of melanoma cells and its impact on treatment of tumors in vivo, which are the expected outcomes of the effects demonstrated unequivocally in the specification.. It is not clear what the purpose is of the "homeostatic regulation in vivo " statement is; everyone knows that normal physiology relies heavily on homeostasis. So what? How does that relate to the present claims and their enablement?*

J. "Further, cancer cells *in vitro* have different properties and characteristics than primary cancer cells, as taught by Drexler *et al.*, Embleton *et al.*, Hsu *et al.*, Freshney *et al.*, and Dermer, all of record, and thus *it is unpredictable that cancer cells in vitro would have the same responses to drugs as primary cancer cells.* Moreover, one cannot extrapolate the *in vitro teaching* of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, as taught by Gura, Jain, Curti, and Hartwell *et al.*, all of record. For the reasons set forth above, and in previous Office Action, the Office maintains its position that one cannot predict that the claimed method would be effective in killing melanoma cells *in vivo*."

Applicants' Additional Remarks on the Enablement Rejection

Applicants' results and those of others cited in the application, in combination with other advances in the art at the time of the present invention, are legally adequate to overcome the old mantra and selective citation and re-citation of the "usual" references that "*in vitro* does not equal *in vivo*" and results *in vitro* cannot predict results in *vivo*. Applicants are further supported by cases such as *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), citing, for example, *In re Krimmel* 130 U.S.P.Q. 215 (CCPA 1961) and *In re Bergel*, 130 U.S.P.Q. (CCPA 1961).

Applicants contend that the specification does provide sufficient support for the claimed invention, as defined by the amended claims. They will not reiterate their "Wands Analysis" from the prior response. To summarize a few key points:

(1) There is no evidence or compelling rationale of record in this case that the nature of the invention and the state of the art that would inherently require an unreasonably excessive amount of experimentation, or that additional or alternative test protocols are necessary to practice Applicants' invention, or that one skilled in the art could not readily implement the methods described in the specification.

(2) The Office Action did not provide any basis to fault specifically the amount of direction or guidance presented in the specification to enable the skilled artisan to practice the present invention as claimed.

(3) The Action does not provide evidence or compelling rationale why the art of cancer therapy is so inherently complex that it does not permit application of information gathered from accepted *in vitro* and animals studies to support claims to killing of cancer cells or therapeutic effects on tumors. The areas of cancer therapy and signal transduction are well studied, and the state of the art is advanced on many fronts. Credit is due to advances in the field of cancer therapy, including immunotherapy, over the last 20 -30 years.

(4) Consideration of the invention as a whole, in view of the disclosure and working examples as well as the understanding in the art about the small organic MEK inhibitor compounds, would reasonably lead a skilled person to conclude that the invention is enabled.

Applicants respectfully remind the Office that the amended claims are directed to administering a member of a family of direct, noncompetitive MEK inhibitors, with emphasis on

PD184352 as well as PD98059 and U0126, that have the unexpected property of killing melanoma cells. Each of these compounds and its properties is described in the specification and the prior art. The inventors found that these agents caused melanoma-selective apoptotic and cytotoxic responses. The specification does set forth a schedule of dosages for these inhibitors which clearly includes PD184352

Applicants reiterate their reminder that according to MPEP 2164.02, an example may be "working" or "prophetic." The experiments and administration of the compounds set forth in application are fully and adequately disclosed in such manner that one skilled in the art can practice the invention to the full extent of the claim scope without requiring undue experimentation. Applicants need not describe every embodiment in order for the disclosure to be enabling. When considering factors relating to a determination of enablement, if all the other factors point toward enablement, then the absence of a working Example will not by itself render the claims non-enabled.

The patent law recognizes the importance of a correlation between *in vitro* results and predicted *in vivo* action of a biological or chemical agent, and this is related to the issue of the presence or absence of working examples. An *in vitro* or *in vivo* animal model exemplified in the specification constitutes a "working example" if that example "correlates" with a disclosed or claimed method. Obviously, the impact of such "correlation" also depends on the state of the prior art. If a particular *in vitro* or animal model is recognized as being correlated to a specific condition, as in the case of melanoma cell lines *in vitro* or growing a tumor xenografts in mice, then it should be accepted as correlating unless the Examiner can come forth with specific evidence for a lack of correlation. Even with such evidence, the Examiner is required to weigh the evidence for and against a correlation and set forth whether one skilled in the art would accept the model as reasonably correlated to the condition. See: *In re Brana, supra*, (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). In view of the initial burden on the Office to give reasons for the lack of enablement, an Examiner must also give the Applicant specific reasons for concluding that an *in vitro* or *in vivo* animal model example **lacks the requisite correlation**. Moreover, there is no hard and fast rule as to how invariable or exact the correlation must be (*Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

Based upon the relevant evidence as a whole, a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity will be found even absent rigorous correlation where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

IV. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are in condition for allowance, and respectfully requests early notice of such favorable action.

Examiner Davis is respectfully requested to contact the undersigned at (202) 496-7845 with any questions or comments if they will assist in the understanding this amendment and response. (The undersigned spoke with the Examiner on the phone since the 5 October 2004 deadline when this response was originally filed and was assured that the Examiner made a note to contact the undersigned to discuss the case before completing the next Action.)[2]

Fees for the extension of time may be charged to the **Deposit Account 50-0911**. . In the unlikely event that the Patent and Trademark Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due to **Deposit Account 50-0911**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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[2] The foregoing sentence has been added in this Supplemental Response

[3] Again, the Office is respectfully requested to note change in correspondence address.